

PATENT SPECIFICATION

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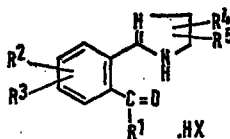


(54) NOVEL IMIDAZOLINE DERIVATIVES

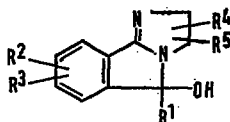
(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain 5-aryl-2,3-dihydro-2,2 (or 3,3)-dialkyl-5H-imidazo[2,1-a]isoindol-5-ols, to processes for preparing them and to pharmaceutical compositions containing them. It particularly concerns pharmacologically active 5-aryl-2,3-dihydro-2,2 (3,3) dimethyl-5-imidazo[2,1-a] isoindol-5-ols and 2-[4,4 (or 5,5)-dimethyl-2-imidazolin-2-yl]benzophenone acid addition salts. The intermediates produced in the processes of the invention are also novel.

The invention provides new compounds having the following formulae



(I)



(II)

wherein R¹ is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R² is hydrogen, halogen, amino, (lower)alkylamino, (lower)alkyl or (lower)alkoxy; R³ is hydrogen when R² and R³ are dissimilar and when R² and R³ are the same they are both selected

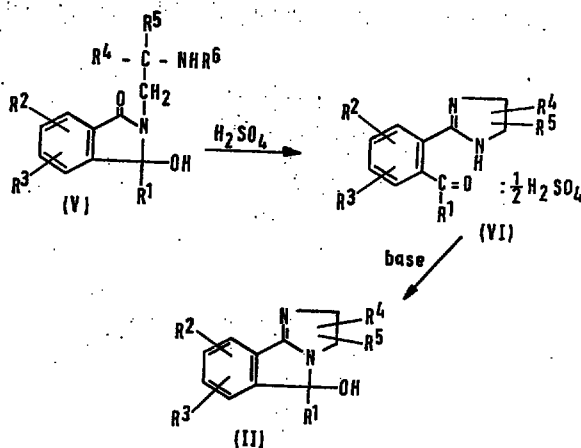
from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; R^4 and R^5 are (lower)alkyl attached to the same carbon atom; and X is an anion portion of a pharmacologically acceptable acid addition salt.

These compounds have useful pharmacological activity and are useful for the preparation of other pharmacologically active compounds. The novel compounds of formulae I and II exhibit anti-depressant activity but unlike the compounds of Specification No. 1,229,652 they do not possess anorectic activity at therapeutic doses. They can also be used as intermediates in the preparation of benzhydrols and related compounds according to British Application No. 46941/70. (Serial No. 1322339)

As employed herein the term "(lower)alkyl" is meant to include straight and branched chain hydrocarbon moieties of from 1 to 4 carbon atoms such as methyl, ethyl, propyl, *i*-propyl and butyl. The term "(lower)alkoxy" is used to include hydrocarbonoxy groups which contain from 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, butoxy and hexoxy. The terms "halogen" and "halo" as used herein are meant to include bromine, fluorine, chlorine and iodine.

Those skilled in the art will appreciate that the compounds of formulae I and II are tautomers. It has been found that the base form (II) exists as the tricyclic imidazoisindole form and the acid addition salt (I) exists as the benzophenone form. The nature of the reaction by which the compounds are prepared does not allow the position of the gem-dialkyl groups to be fixed with certainty. When the compound exists as the benzophenone type form, it is impossible to fix the position of the gem-dialkyl groups because of the proton shift due to the —NH—C=N— group. Hence, the 2-(gem-dialkyl-2-imidazolin-2-yl)benzophenone acid addition salts are named as 4,4(5,5)-dialkyl substituted compounds. This is in conformity with the nomenclature for imidazole compounds set forth in Heterocyclic Compounds, R. C. Elderfield, Editor, Vol. 5., pp 198, 199 and 238, John Wiley & Sons, Inc., New York, 1957. When the imidazoisindol-ol form of tautomer is formed, the tautomerism of the HN—C=N— moiety does not permit any absolute prediction as to positioning of the gem-dialkyl group. When the steric influence of the gem-dialkyl group is considered, the probability is great that the product obtained is a 2,2-dialkyl compound. Gas chromatographic studies indicate a single compound is isolated and not a mixture of the 2,2-dialkyl and 3,3-dialkyl isomers. As the available evidence does not conclusively eliminate the possibility of the formation of the 3,3-dialkyl compound, the alternative nomenclature is employed herein, although it is believed that the structure is in actuality a 2,2-dialkyl-5H-imidazo-[2,1-a]isoindol-5-ol.

The compounds of formulae I and II may be prepared by contacting the appropriate phthalimidine with a strong acid such as sulphuric acid and, if desired, subsequently treating the product with base:

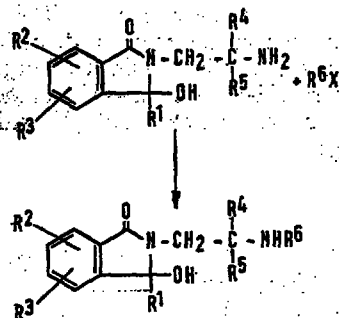


wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same as herein above defined and R^6 is an organosulphonyl group. R^6 is preferably a (lower)alkylsulphonyl, phenylsulphonyl, monohalophenylsulphonyl, dihalophenylsulphonyl, mono(lower)alkylphenylsulphonyl, di(lower)alkylphenylsulphonyl or (lower)alkoxyphenylsulphonyl. The compounds having general formula V are described and claimed in our Application No. 20997/72. (Serial No. 1325066)

Concentrated sulphuric acid of 75—100% strength is employed in converting compound V to compound VI. Generally, no criticality attaches to the use of a

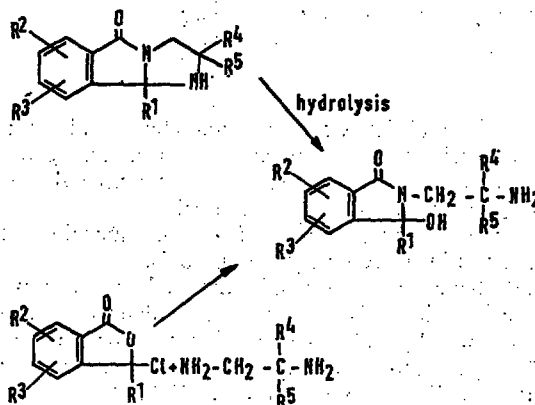
particular basic compound when the sulphate salt is treated to prepare the imidazoisindol-ol base form. For example, sodium carbonate, sodium hydroxide, potassium hydroxide or sodium bicarbonate may be used. When the tautomeric acid addition salt is to be prepared, the preferred method is to saturate a lower alkanolic solution of the base form of the compound with hydrogen chloride gas. Suitable lower alkanols include methanol, ethanol and propanol.

The intermediate sulphonated phthalimidines may be prepared as follows:



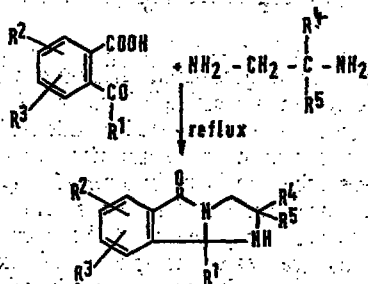
wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as above defined and X is a halogen atom. The sulphonation is usually conducted in pyridine, e.g. at 25°C to 115°C for 4 to 8 hours, although other suitable organic or aqueous solvents with a base such as sodium carbonate or triethylamine may be employed. The reactants can be refluxed for about 12 to 24 hours, then the solvent is evaporated and the residue is partitioned between water and an immiscible organic solvent such as ethyl acetate, ether, chloroform or benzene. The organic portion is separated and then the solvent is evaporated. The residue is recrystallized from a lower alkanol such as methanol, ethanol or propanol to yield the sulphonated product.

The phthalimidines may be obtained by the hydrolysis of an imidazoisindolone or by reaction of the ψ -acid chloride of an *o*-aroyl-benzoic acid with the appropriate 1,1-dialkylethylenediamine:



wherein R¹, R², R³, R⁴, R⁵ and R⁶ are the same as hereinabove defined.

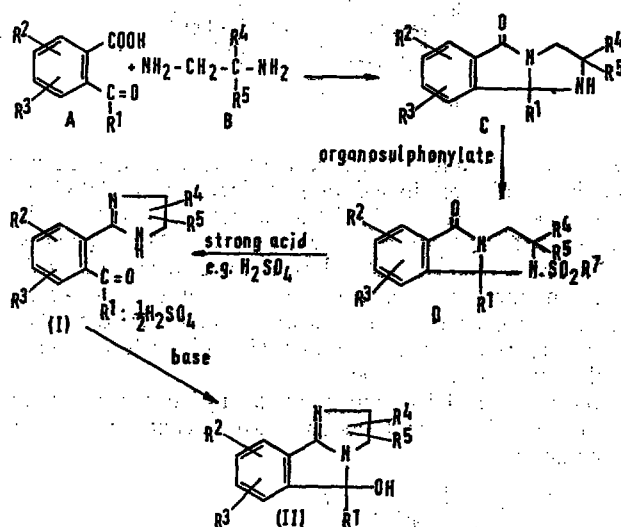
The imidazoisindolone compounds may be prepared by condensing a 1,1-dialkylethylenediamine with the appropriate *o*-(aroyl)benzoic acid:



wherein R¹, R², R³, R⁴ and R⁵ are the same as hereinabove defined.

The imidazoisindolones may be prepared by refluxing the reactants in a water-immiscible organic solvent such as toluene, benzene, xylene, chloroform, carbon tetrachloride or pyridine. The flask should be equipped with a water separator and the usual period of reflux is 12—24 hours. The solution is then extracted with water and the organic layer is evaporated *in vacuo* to a solid residue. On recrystallization from ethanol, ethyl acetate, hexaneacetone or chloroform, the imidazoisindolone is obtained in good yield.

The compounds of formulae I and II can also be prepared by treating a 9b-aryl-2,2-dialkyl-1,2,3,9b-tetrahydro-1-(organosulphonyl)-5H-imidazo[2,1-a]isindol-5-one (D) with a strong acid such as sulphuric acid, and, if desired, forming the free base form II. The compounds D can be obtained by organo-sulphonylating a 9b-aryl-2,2-dialkyl-1,2,3-9b-tetrahydro-5H-imidazo[2,1-a]-isindol-5-one (C) which in turn is prepared by condensing an aroylbenzoic acid (A) with a 1,2-alkylene diamine (B) as indicated by the following:



wherein R¹, R², R³, R⁴ and R⁵ are as defined above and R⁷ is an organic residue, e.g. a substituted or unsubstituted hydrocarbon group, e.g. (lower)alkyl, phenyl, monoalkylphenyl, dihalophenyl, monoalkylphenyl or dialkylphenyl (that is, R₇SO₂— is an organosulphonyl residue whose nature is not critical).

The compounds of formulae I and II are pharmacologically active as anti-depressant agents when administered orally to mammals.

The compounds have been orally administered to a group of six mice (3 males and 3 females). One hour later the animals are challenged with reserpine, 2.5 mg./kg. administered intraperitoneally. The degree of ptosis for each eye was determined at one and two hours post treatment. Prevention of reserpine ptosis is an indication of anti-depressant activity. See Rubin et al, J.P.E.T. 120, 125 (1957). Controls are simultaneously run with amphetamine and imipramine. The compounds of formulae I and II were found to be active in mice at a dose of about 0.95 mg./kg. when administered orally.

The compounds have also been tested for anorexic activity according to the following procedure:

Male Charles River rats of between 120 and 140 grams are trained to drink sweetened condensed milk from a graduated drinking tube. After a short learning period the animals are placed on a routine of water *ad lib* for 24 hours, standard laboratory chow for 22 hours and sweetened condensed milk for 2 hours. The volume of milk consumed is measured at 30 minutes as well as 2 hours. The animals are weighed every day. This schedule is maintained 5 days a week over a period of several months. Drug trials are run on Thursdays and changes in milk consumed and 24 hour weight changes are compared with the average of the two days before drug administration. Animals are tested as groups of six and one group is given saline each week to serve as control. Drugs are usually administered intraperitoneally in saline or orally in water.

The compounds of the invention did not inhibit appetite when treated at dosage levels of up to 10 mg./kg. of body weight, P.O.

The compounds of formulae I provided by the invention contain basic nitrogen atoms forming acid-addition salts with pharmaceutically acceptable acids and the invention also provides such salts. Suitable acids for the formation of acid-addition salts include hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, lactic, citric, tartaric, maleic, gluconic, benzenesulphonic, toluenesulphonic and methylsulphonic acids.

The invention further provides a pharmaceutical composition which comprises a compound provided by the invention, which may for example be micronised, and a pharmaceutically acceptable non-toxic carrier.

Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99%, preferably 10—80%, by weight of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, a sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 1 mg. or less to 500 mg. or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

When the compounds of formulae I and II are employed as anti-depressant compounds, they may be administered to mammals, e.g. mice, rats, rabbits, dogs, cats, monkeys, etc. alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in the solid form containing such excipients as starch, milk, sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of these compounds will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular sub-

ject under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

The following examples have been added to illustrate the invention:

EXAMPLE 1.

A solution of 50 g. of *o*-(*p*-chlorobenzoyl)benzoic acid, 100 ml. of toluene and 40 ml. of 1,2-diamino-2-methyl-propane is refluxed in a flask equipped with a water separator. After refluxing for seventeen hours, the solution is extracted with water and the organic portions evaporated *in vacuo* to a solid residue. On recrystallization from ethanol, there is obtained 9b-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 132—40°C.

Anal. Calc'd for $C_{18}H_{17}ClN_2O$: C, 69.34; H, 5.17; N, 8.99; Cl, 11.11.
Found: C, 69.21; H, 5.40; N, 8.65; Cl, 11.30.

In a similar manner, reacting appropriate 1,1-dialkylethylene diamines with *o*-benzoylbenzoic acids, there are obtained:

1,2,3,9b-tetrahydro-2,2-diethyl-9b-phenyl-5H-imidazo[2,1-*a*]isoindol-5-one;
2,2 - diethyl - 9b - (3,4 - diiodophenyl) - 1,2,3,9b - tetrahydro - 5H - imidazo[2,1-*a*]isoindol-5-one;
9b - (3,4 - diethoxyphenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H - imidazo[2,1-*a*]isoindol-5-one;
7 - amino - 9b - (*p* - fluorophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dipropyl - 5H-imidazo[2,1-*a*]isoindol-5-one; and
7 - chloro - 9b - (4 - ethylphenyl) - 1,2,3,9b - tetrahydro - 2 - methyl - 2-propyl-5H-imidazo[2,1-*a*]isoindol-5-one.

EXAMPLE 2.

A solution of 50 g. of *o*-(*p*-fluorobenzoyl)benzoic acid, 150 ml. of toluene and 75 ml. of 1,2-diamino-2-methylpropane is refluxed in a flask equipped with a water separator. After refluxing for nineteen hours the solution is extracted with water. The toluene layer is evaporated to dryness and the residue is recrystallized from aqueous alcohol to obtain 9b-(*p*-fluorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 108—110°C.

Anal. Calc'd for $C_{18}H_{17}F_2N_2O$: C, 72.95; H, 5.78; N, 9.45.
Found: C, 72.83; H, 5.86; N, 9.45.

Similarly, 1,2,3,9b - tetrahydro - 2,2,7 - trimethyl - 9b - phenyl - 5H - imidazo[2,1-*a*]isoindol-5-one; and 1,2,3,9b-tetrahydro-2,2-dimethyl-9b-phenyl-9-propyl-5H-imidazo[2,1-*a*]isoindol-5-one are prepared.

EXAMPLE 3.

A solution of 40 g. of *o*-benzoylbenzoic acid, 60 ml. of 1,2-diamino-2-methyl-propane, and 150 ml. of toluene is refluxed in a flask equipped with a water separator. After refluxing eight hours the solution is extracted with water and the toluene portion is evaporated to dryness. The residue is recrystallized from ethanol to obtain 1,2,3,9b - tetrahydro - 9b - phenyl - 2,2 - dimethyl - 5H - imidazo[2,1 - *a*]isoindol-5-one, m.p. 146—9°C.

Anal. Calc'd for $C_{18}H_{17}N_2O$: C, 77.67; H, 6.52; N, 10.07.
Found: C, 77.35; H, 6.88; N, 10.15.

Repeating the above procedure, the following compounds are prepared:

9b - (3,4 - dichlorophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H-imidazo[2,1-*a*]isoindol-5-one;
2,2 - diethyl - 9b - (*p* - fluorophenyl) - 1,2,3,9b - tetrahydro - 5H - imidazo[2,1-*a*]isoindol-5-one; and
1,2,3,9b-tetrahydro-2,2-dimethyl-9b-(*p*-tolyl)-5H-imidazo[2,1-*a*]isoindol-5-one.

EXAMPLE 4.

A solution of 35 g. of *o*-(*p*-bromobenzoyl)benzoic acid, 125 ml. of toluene, and 50 ml. of 1,2-diamino-2-methylpropane is refluxed in a flask equipped with a water separator. After refluxing six hours, the solution is extracted with water. The toluene layer is evaporated to dryness *in vacuo*. On recrystallization from dilute alcohol there

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is obtained 9b - (*p*-bromophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 135—5°C.

Anal. Calc'd for $C_{18}H_{17}N_2BrO$: C, 60.51; H, 4.80; N, 7.84.

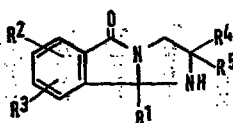
Found: C, 60.80; H, 4.91; N, 7.91.

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EXAMPLE 5.

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When the procedure of Examples 1—4 is repeated to condense an appropriate 1,1-dialkylethylene diamine with an *o*-aroylbenzoic acid, the following 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones are produced:



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wherein R¹, R², R³, R⁴ and R⁵ are as follows:

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R ¹	R ²	R ³	R ⁴	R ⁵
<i>p</i> -iodophenyl	7-bromo	hydrogen	methyl	methyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl
2-thienyl	7-methoxy	8-methoxy	<i>n</i> -butyl	<i>n</i> -butyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl
2-pyridyl	7-fluoro	8-fluoro	methyl	<i>n</i> -butyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl
2-furyl	7-ethyl	hydrogen	methyl	methyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl
phenyl	8-ethyl	hydrogen	methyl	methyl
2,5-di- <i>n</i> -butylphenyl	hydrogen	hydrogen	methyl	methyl
phenyl	hydrogen	hydrogen	ethyl	methyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl

EXAMPLE 6.

A mixture of 30 g. of 9b-(p-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example I, and 100 ml. of 50% hydrochloric acid is heated in a steam bath. Dissolution occurs on heating for ten minutes; and then a solid begins to precipitate immediately. The mixture is cooled, filtered and washed with acetone to obtain 2-(2-amino-2-methylpropyl)-3-(p-chlorophenyl)-3-hydroxyphthalimidine hydrochloride, m.p. 230—2°C.

This hydrochloride salt is neutralized with sodium carbonate solution to obtain the corresponding phthalimidine base, m.p. 208—10°C., (recrystallized from ethanol). *Anal.* Calc'd for $C_{14}H_{19}N_2ClO_2$: C, 65.35; H, 5.79; N, 8.47; Cl, 10.72. Found: C, 65.48; H, 5.75; N, 8.43; Cl, 10.88.

Similarly, the following compounds are prepared from other 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-ones of Example I:

2-(2-amino-2-ethylbutyl)-3-hydroxy-3-(3,4-diiodophenyl)phthalimidine;

2-(2-amino-2-methylpropyl)-3-(3,4-diethoxyphenyl)-3-hydroxyphthalimidine;

6-amino-2-(2-amino-2-propylpentyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine;

and

2-(2-amino-2-methylpentyl)-6-chloro-3-(p-ethylphenyl)-3-hydroxyphthalimidine.

EXAMPLE 7.

A mixture of 45 g. of 9b-(p-fluorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example 2, and 150 ml. of 50% hydrochloric acid is heated in a steam bath. After ten minutes a clear solution forms; then solid begins to precipitate. The mixture is heated for an additional ten minutes, and then cooled, filtered and washed with acetone. The solid obtained is 2-(2-amino-2-methylpropyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine hydrochloride, hydrate, m.p. 177—180°C. dec.

The hydrochloride salt is neutralized with sodium carbonate solution to obtain the phthalimidine base, m.p. 196—9°C.

Anal. Calc'd for $C_{14}H_{19}N_2FO_2$: C, 68.78; H, 6.09; N, 8.91.

Found: C, 68.83; H, 6.18; N, 8.99.

Similarly 2-(2-amino-2-methylpropyl)-3-hydroxy-6-methyl-3-phenylphthalimidine; and 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenyl-4-propylphthalimidine are prepared.

EXAMPLE 8.

A mixture of 48 g. of 1,2,3,9b-tetrahydro-9b-phenyl-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example 3, and 150 ml. of 50% hydrochloric acid is heated on a steam bath. A clear solution forms within fifteen minutes and then reprecipitation occurs. After heating an additional five minutes, the mixture is cooled and filtered to obtain 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenylphthalimidine hydrochloride, m.p. 252—5°C. (dec.).

The above-prepared hydrochloride salt is neutralized with sodium carbonate solution to obtain the phthalimidine base, m.p. 172—3°C.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45.

Found: C, 72.80; H, 6.93; N, 9.32.

Repeating the above procedure, the following compounds are prepared:

2-(2-amino-2-methylpropyl)-3-(3,4-dichlorophenyl)-3-hydroxyphthalimidine;

2-(2-amino-2-ethylbutyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine; and

2-(2-amino-2-methylpropyl)-3-hydroxy-3-(p-tolyl)-phthalimidine.

EXAMPLE 9.

A mixture of 33 g. of 9b-(p-bromophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one and 120 ml. of 50% hydrochloric acid is heated in a steam bath. A clear solution forms within ten minutes and then reprecipitation occurs. After heating an additional ten minutes, the mixture is cooled and filtered to obtain 2-(2-amino-2-methylpropyl)-3-(p-bromophenyl)-3-hydroxyphthalimidine hydrochloride, m.p. 227—230°C. (dec.).

The above-prepared hydrochloride salt is neutralized with sodium carbonate solution to obtain the phthalimidine base, m.p. 194—6°C.

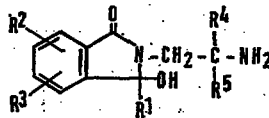
Anal. Calc'd for $C_{18}H_{19}N_2BrO_2$: C, 57.61; H, 5.10; N, 7.46.

Found: C, 57.37; H, 5.19; N, 7.29.

EXAMPLE 10.

When the procedure of Examples 6—9 is repeated to hydrolyze an appropriate 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one, as described in Example 5, the corresponding 2-(2-amino-2,2-dialkylethyl)-3-aryl-3-

hydroxyphthalimidine hydrohalide is afforded, which is then neutralized to produce the base thereof having the formula:



wherein R¹, R², R³, R⁴ and R⁵ are as follows:

R ¹	R ²	R ³	R ⁴	R ⁵
<i>p</i> -iodophenyl		7-bromo	hydrogen	methyl
3,4-dimethylphenyl		8-methoxy	hydrogen	ethyl
<i>p</i> -methoxyphenyl		7-chloro	8-chloro	methyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl		7-methylamino	hydrogen	ethyl
2,5-dibromophenyl		7-methyl	8-methyl	methyl
3,4-dimethoxyphenyl		6-ethoxy	hydrogen	methyl
2-thienyl		7-methoxy	8-methoxy	<i>n</i> -butyl
<i>p</i> -propoxyphenyl		9-iodo	hydrogen	methyl
2-pyridyl		7-fluoro	8-fluoro	<i>n</i> -butyl
2,5-dipropoxyphenyl		hydrogen	hydrogen	methyl
2-furyl		7-ethyl	hydrogen	methyl
3,4-diethylphenyl		8-propylamino	hydrogen	methyl
5,6,7,8-tetrahydro-2-naphthyl		7-ethyl	9-ethyl	ethyl
<i>o</i> -chlorophenyl		hydrogen	hydrogen	methyl
phenyl		8-ethyl	hydrogen	methyl
2,5-di- <i>n</i> -butylphenyl		hydrogen	hydrogen	methyl
phenyl		hydrogen	hydrogen	methyl
<i>p</i> -chlorophenyl		7-ethoxy	hydrogen	methyl
<i>m</i> -chlorophenyl		hydrogen	hydrogen	methyl

EXAMPLE 11.

24 The ψ -acid chloride prepared from 26 g. of *o*-(*p*-chlorobenzoyl)benzoic acid is dissolved in 40 ml. of acetone and is added dropwise with stirring to 35 ml. of 1,2-diamino-2-methylpropane and 150 ml. of pyridine. The mixture is stirred and re-fluxed for one hour and then evaporated to dryness *in vacuo*. The residue is slurried with water and separated by filtration. On recrystallization from ethanol there is obtained 2-(2-amino-2-methylpropyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine, m.p. 208—210°C.

In a similar manner, the ψ -acid halides of the appropriate *o*-benzoylbenzoic acids are acylated to afford the following compounds:

2-(2-amino-2-methylpropyl)-3-(*p*-fluorophenyl)-3-hydroxyphthalimidine, m.p. 177—180°C.;

2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenylphthalimidine, m.p. 172—3°C.; and

2-(2-amino-2-methylpropyl)-3-(*p*-bromophenyl)-3-hydroxyphthalimidine, m.p. 194—6°C.

EXAMPLE 12.

A mixture of 30 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine hydrochloride, as prepared in Example 6, 30 g. of *p*-toluenesulphonyl chloride and 500 ml. of anhydrous pyridine is refluxed eighteen hours. The mixture is evaporated to dryness. The residue is partitioned between ethyl acetate and water. The ethyl acetate portion is dried over magnesium sulphate and then evaporated to dryness to a solid residue. On recrystallization from ethanol, there is obtained 9b-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-1-(*p*-tolylsulphonyl)-5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 184—6°C.

Anal. Calc'd for $C_{25}H_{23}ClN_2O_3S$: C, 64.24; H, 4.97; N, 6.00; Cl, 7.60; S, 6.87. Found: C, 63.99; H, 4.83; N, 6.07; Cl, 7.60; S, 6.80.

A solution of 10 g. of the above-prepared 9b-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-1-(*p*-tolylsulphonyl)-5H-imidazo[2,1-*a*]isoindol-5-one and 25 ml. of 85% sulphuric acid is allowed to stand at room temperature for two hours. The reaction mixture which contains the sulphate salt of 4-chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several times its volume of ice-water and made basic with concentrated sodium hydroxide solution. The precipitated solid is separated and washed with water. On recrystallization from ethanol there is obtained 5-(*p*-chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-*a*]isoindol-5-ol, m.p. 201—3°C.

Anal. Calc'd for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.49; N, 8.96; Cl, 11.34. Found: C, 68.98; H, 5.41; N, 9.05; Cl, 11.49.

IR (KBr) 1637 cm^{-1} , 2222—2739 cm^{-1}

U.V. (95% EtOH) max. 222m μ ($\epsilon=22,200$)
max. 263m μ ($\epsilon=6,000$)
max. 272m μ ($\epsilon=5,700$)
(pH 1) max. 263m μ ($\epsilon=12,960$)

The compound of Example 12 possesses in addition to its anti-depressant activity the property of markedly reducing sleep at dosage levels which produce no signs of agitation or stimulation.

EXAMPLE 13.

A mixture of 35 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine hydrochloride, as prepared in Example 6, 25 g. of *p*-toluenesulphonyl chloride and 125 ml. of anhydrous pyridine is refluxed for three hours. The solution is evaporated to dryness and the residue partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to a solid residue. On recrystallization from ethanol there is obtained *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide, m.p. 225—7°C.

Anal. Calc'd for $C_{25}H_{25}ClN_2O_4S$: C, 61.91; H, 5.20; N, 5.78; Cl, 7.31; S, 6.61. Found: C, 61.83; H, 5.00; N, 5.63; Cl, 7.43; S, 6.82.

A solution of 15 g. of the above-prepared *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide and 40 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The reaction mixture which contains the sulphate salt of 4'-chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several times its volume of ice-water and neutralized with concentrated sodium hydroxide solution. The solid is

separated and washed with water. On recrystallization there is obtained 5-(*p*-chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 199—202°C., identical by the usual criteria to that obtained in Example 12.

A suspension of 1.5 g. of the above-prepared 5-(*p*-chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol in 25 ml. of absolute ethanol is saturated with hydrogen chloride. The solution is evaporated to dryness *in vacuo*. The residue is triturated with ethyl acetate and separated by filtration. On recrystallization from an ethanol-ethyl acetate, there is obtained 4'-chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 235—8°C. dec.

Anal. Calc'd for $C_{18}H_{17}N_2OCl.HCl$: C, 61.90; H, 5.19; N, 8.20; Cl, 20.30.

Found: C, 61.59; H, 5.29; N, 8.20; Cl, 20.53.

IR (KBr) 1670 cm^{-1} , 2558—2941 cm^{-1} .

U.V. (Isopropanol) max. 263 $m\mu$ ($\epsilon=12,460$)

EXAMPLE 14.

A mixture of 32 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-fluorophenyl)-3-hydroxy-phthalimidine, 22 g. of *p*-toluenesulphonyl chloride and 200 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness *in vacuo* and the residue is partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to dryness. The residue is recrystallized from ethanol to obtain *N*-(2-[3-(*p*-fluorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluene-sulphonamide, m.p. 206—9°C.

Anal. Calc'd for $C_{25}H_{25}N_2FSO_4$: C, 64.09; H, 5.37; N, 6.30.

Found: C, 64.25; H, 5.39; N, 6.30.

A solution of 22 g. of *N*-(2-[3-(*p*-fluorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluene-sulphonamide in 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The mixture which contains the sulphate salt of 4'-fluoro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)-benzophenone is quenched with several times its volume of ice-water and neutralized with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallization from ethyl acetate there is obtained 5-(*p*-fluorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 194—6°C.

Anal. Calc'd for $C_{18}H_{17}N_2FO$: C, 72.96; H, 5.78; N, 9.45.

Found: C, 72.88; H, 5.91; N, 9.45.

IR (KBr) 1658 cm^{-1} , 2273—2278 cm^{-1}

U.V. (95% of EtOH) max 260 $m\mu$ ($\epsilon=5,760$)

max 272 $m\mu$ ($\epsilon=5,000$)

(pH1) max 252 $m\mu$ ($\epsilon=13,000$)

On treating 5-(*p*-fluorophenyl)-2,3-dihydro-2,2-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride, there is obtained 4'-fluoro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 203—5°C.

Anal. Calc'd for $C_{18}H_{17}N_2FO.HCl$: C, 64.96; H, 5.45; N, 8.42.

Found: C, 64.79; H, 5.47; N, 8.39.

IR (KBr) 1658 cm^{-1} , 2600—2941 cm^{-1}

U.V. (isopropanol) max 250 $m\mu$ ($\epsilon=12,100$)

EXAMPLE 15.

A mixture of 27.5 g. of 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenyl-phthalimidine, 20 g. of *p*-toluenesulphonyl chloride and 200 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness. The residue is triturated with water and separated by filtration. On recrystallization from 95% ethanol there is obtained *N*-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluene-sulphonamide, m.p. 197—200°C.

Anal. Calc'd for $C_{25}H_{26}N_2SO_4$: C, 66.64; H, 5.81; N, 6.22.

Found: C, 66.30; H, 5.70; N, 6.13.

A solution of 17 g. of *N*-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide in 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The solution which contains the sulphate salt of 2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several times its volume of ice-water and neutralized with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallization from

ethanol there is obtained 5-phenyl-2,3-dihydro-2,2-dihydro-2,2 (or 3,3-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol, m.p. 211—212°C.

Anal. Calc'd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07.

Found: C, 77.44; H, 6.64; N, 9.87.

5 IR (KBr) 1645 cm^{-1} , 2273—2790 cm^{-1}
 U.V. (95% EtOH) max 260 $\text{m}\mu$ ($\epsilon=4,900$)
 max 272 ($\epsilon=4,440$)
 (pH1) max 250 $\text{m}\mu$ ($\epsilon=13,480$)

10 On treating 5-phenyl-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol with hydrogen chloride, there is obtained 2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)-benzophenone; hydrochloride, m.p. 174—6°C.

Anal. Calc'd for $C_{18}H_{18}N_2O \cdot HCl$: C, 68.68; H, 6.08; N, 8.90.

Found: C, 68.86; H, 6.07; N, 8.87.

15 IR (KBr) 1645 cm^{-1} , 2564—3077 cm^{-1}
 U.V. (isopropanol) max. 249 $\text{m}\mu$ ($\epsilon=12,940$)

EXAMPLE 16.

20 A mixture of 16.8 g. of 2-(2-amino-2-methylpropyl)-3-(p-bromophenyl)-3-hydroxyphthalimidine, 10 g. of p-toluene-sulphonyl chloride and 100 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness and the residue is partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to a solid residue. On recrystallization from ethanol there is obtained N-(2-[3-(p-bromophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-p-toluenesulphonamide, m.p. 234—7°C.

Anal. Calc'd for $C_{25}H_{25}N_2BrSO_4$: C, 56.71; H, 4.76; N, 5.30.

25 Found: C, 56.91; H, 4.65; N, 5.45.

30 A solution of 11 g. of N-(2-[3-(p-bromophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-p-toluenesulphonamide and 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The solution which contains the sulphate salt of 4'-bromo-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several times its volume of ice-water and neutralized with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallization from ethyl acetate, there is obtained 5-(p-bromophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol, m.p. 192—4°C.

Anal. Calc'd for $C_{18}H_{17}N_2BrO$: C, 60.51; H, 4.79; N, 7.85.

35 Found: C, 60.51; H, 4.82; N, 7.82.

40 IR (KBr) 1639 cm^{-1} , 2273—2778 cm^{-1}
 U.V. (95% EtOH) max. 224 $\text{m}\mu$ ($\epsilon=24,400$)
 max. 263 $\text{m}\mu$ ($\epsilon=6,780$)
 max. 275 $\text{m}\mu$ ($\epsilon=6,400$)
 (pH1) max. 267 $\text{m}\mu$ ($\epsilon=13,640$)

On treating 5-(p-bromophenyl)-2,3-dihydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol with hydrogen chloride there is obtained 4'-bromo-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone, hydrochloride. m.p. 222—5°C.

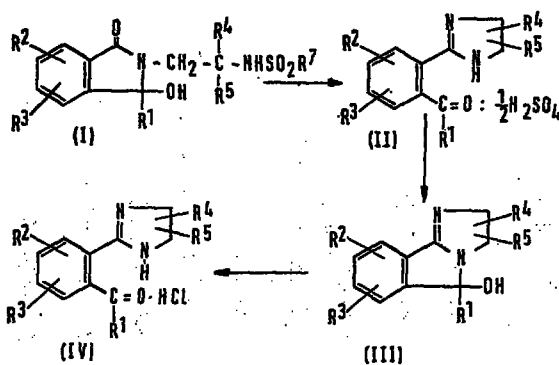
Anal. Calc'd for $C_{18}H_{17}BrN_2O \cdot HCl$: C, 54.91; H, 4.61; N, 7.12.

45 Found: C, 55.09; H, 4.67; N, 6.75.

IR (KBr) 1661 cm^{-1} , 2500—2941 cm^{-1}
 U.V. (Isopropanol) max. 267 $\text{m}\mu$ ($\epsilon=14,500$)

EXAMPLE 17.

50 When the procedure of Examples 13—16 is repeated to react the appropriate 2-(2-amino-2-alkylalkyl-3-aryl-3-hydroxyphthalimidine hydrohalide with an aryl or alkyl sulphonyl halide, there are afforded the following N-([3-aryl-3-hydroxy-2-phthalimidinyl]-1,1-dialkylalkyl)sulphonamides (I) which are then contacted with sulphuric acid to afford appropriate sulphate salts of 4,4(5,5)-dialkyl-2-imidazolin-2-yl phenyl aryl ketone compounds (II) which are neutralized to afford appropriate 2,2(or 3,3)-dialkyl-5-aryl-2,3-dihydro-5H-imidazo[2,1-a]isoindol-5-ols (III) which may be acidified, e.g. with hydrochloric acid, to afford the corresponding 4,4(5,5)-dialkyl-2-imidazolin-2-yl-phenyl aryl ketone acid-addition salts (IV), e.g. the hydrochlorides, which compounds (I), (II), (III) and (IV) are depicted by the following formulae:



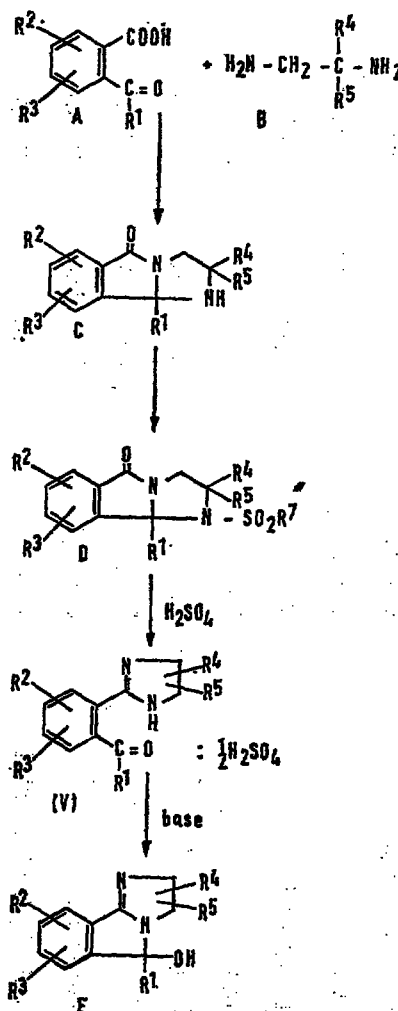
wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are defined below:

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁷
<i>p</i> -iodophenyl	7-bromo	hydrogen	methyl	methyl	ethyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl	phenyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl	<i>p</i> -chlorophenyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl	phenyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl	<i>p</i> -bromophenyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl	4-ethylphenyl
2-thienyl	7-methoxy	8-methoxy	<i>n</i> -butyl	<i>n</i> -butyl	3,4-dimethylphenyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl	phenyl
2-pyridyl	7-fluoro	8-fluoro	methyl	<i>n</i> -butyl	2,5-dichlorophenyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl	<i>n</i> -pentyl
2-furyl	7-ethyl	hydrogen	methyl	methyl	3,4-dibromophenyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl	<i>p</i> -iodophenyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl	<i>p</i> -methoxyphenyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -iodophenyl
phenyl	8-ethyl	hydrogen	methyl	methyl	3,4-difluorophenyl
2,5-di- <i>n</i> -butylphenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl
phenyl	hydrogen	hydrogen	ethyl	methyl	3,4-diethylphenyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl	<i>p</i> -fluorophenyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl

EXAMPLE 18.

A solution of 25 g. of the aroylbenzoic acid A, 75 ml. of toluene and 40 ml. of the gem-dialkylsubstituted 1,2-diamine B is refluxed in a flask equipped with a water separator. After refluxing for 19 hours the solution is extracted with water, and then evaporated to dryness. The residue comprises the 9b-aryl-2,2-dialkyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one C as the major product 38 g. of this product and 32 g. of *p*-toluenesulphonyl chloride in 125 ml. of pyridine are refluxed for 19 hours. The mixture is evaporated to dryness and the residue is dissolved in 100 ml. ethanol. After standing 18 hours the solid is collected and recrystallised to give the 9b-aryl-2,2-dialkyl-1,2,3,9b-tetrahydro-1-(*p*-tolylsulphonyl)-5H-imidazo[2,1-a]-isoindol-5-one D.

A solution of the last mentioned compound D, 25 g., in 90% sulphuric acid (100 ml.) is allowed to stand at room temperature for 45 minutes. The mixture is quenched with several times its volume of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water and crystallised from a suitable crystallisation solvent, e.g. ethanol, to give the 5-aryl-2,3-dihydro-2,2(or 3,3)-dialkyl-5H-imidazo[2,1-a]isoindol-5-ol E. The representative values for R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are given in the attached table. The following compounds are thereby prepared:



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are defined as follows:

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
<i>p</i> -iodophenyl	7-bromo	hydrogen	methyl	methyl	ethyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl	phenyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl	<i>p</i> -chlorophenyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl	phenyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl	<i>p</i> -bromophenyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl	4-ethylphenyl
2-thienyl	7-methoxy	8-methoxy	<i>n</i> -butyl	<i>n</i> -butyl	3,4-dimethylphenyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl	phenyl
2-pyridyl	7-fluoro	8-fluoro	methyl	<i>n</i> -butyl	2,5-dichlorophenyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl	<i>n</i> -pentyl
2-furyl	7-ethyl	hydrogen	methyl	methyl	3,4-dibromophenyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl	<i>p</i> -iodophenyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl	<i>p</i> -methoxyphenyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -iodophenyl
phenyl	8-ethyl	hydrogen	methyl	methyl	3,4-difluorophenyl
2,5-di- <i>n</i> -butylphenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl
phenyl	hydrogen	hydrogen	ethyl	methyl	3,4-diethylphenyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl	<i>p</i> -fluorophenyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl



* C L N S *

31

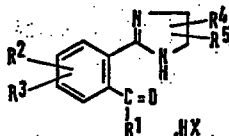
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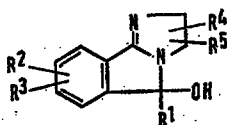
WHAT WE CLAIM IS:—

1. A compound having the general formula:



(I)

or



(II)

wherein R¹ is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8 - tetrahydro - 2 - naphthyl; R² is hydrogen, halogen, amino, lower(alkyl)amino, (lower)alkyl or (lower)alkoxy; R³ is hydrogen when R² and R³ are dissimilar and when R² and R³ are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; R⁴ and R⁵ are (lower)alkyl attached to the same carbon atom and X is an anion portion of a pharmacologically acceptable acid addition salt.

2. A compound according to Claim 1 in which R⁴ and R⁵ are methyl groups.3. A compound according to Claim 1 or 2, wherein R² and R³ are both hydrogen atoms.

4. 5-(p-Chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol.

5. 4'-Chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)-benzophenone hydrochloride.

6. 5-(p-Fluorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol.

7. 4'-Fluoro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)-benzophenone hydrochloride.

8. 5-Phenyl-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol.

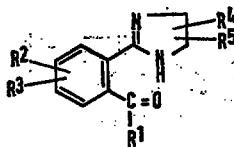
9. 2-(4,4(5,5)-Dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride.

10. 5-(p-Bromophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5H-imidazo[2,1-a]isoindol-5-ol.

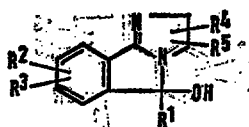
11. 4'-Bromo-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride.

12. A compound according to Claim 1 substantially as described herein and shown with reference to the examples.

13. A process for the preparation of an acid addition salt form of compound of the formula

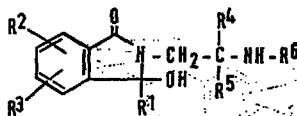


with a strong acid or a compound having the general formula:



(II)

wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined in Claim 1, which comprises treating a compound of the formula:



wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same as defined above and R^6 is an organo-sulphonyl group, with a strong acid to form the aforesaid acid addition salt and, if a compound of formula II is desired, contacting the salt with a base.

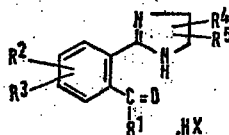
14. A process according to Claim 13, in which R^4 and R^5 are both methyl groups.

15. A process according to Claim 13 or 14, in which R^2 and R^3 are both hydrogen atoms.

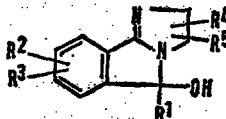
16. A process according to any one of Claims 13 to 15, in which the strong acid used is sulphuric acid.

17. A process according to any one of Claims 13 to 16, wherein R^6 is (lower) alkylsulphonyl, phenylsulphonyl, monohalophenylsulphonyl, dihalophenylsulphonyl, mono(lower)alkylphenylsulphonyl, di(lower)alkylphenylsulphonyl or (lower)alkoxyphenylsulphonyl.

18. A process for the preparation of acid addition salts having the general formula:



wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in Claim 1, which comprises contacting a compound having the formula:

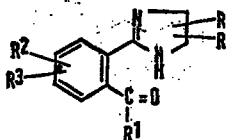


wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same as defined above, with a pharmacologically acceptable acid.

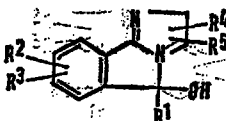
19. A process according to Claim 18, wherein R^4 and R^5 are both methyl groups.

20. A process according to Claim 18 or 19, wherein R^2 and R^3 are both hydrogen atoms.

21. A process for the preparation of an acid addition form of compound of formula



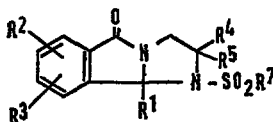
with a strong acid or a compound having the general formula



(II)



wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined in Claim 1, which comprises treating a compound of general formula:



where R^1 , R^2 , R^3 , R^4 and R^5 are as defined above and SO_2R^7 is an organosulphonyl group, with a strong acid, and, if a compound of formula II is desired, treating the product with a base.

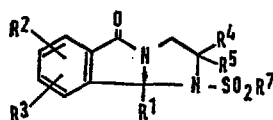
22. A process according to Claim 21, wherein R^4 and R^5 are both methyl groups.

23. A process according to Claim 21 or 22, wherein R^2 and R^3 are both hydrogen atoms.

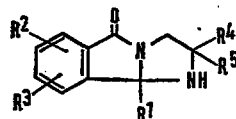
24. A process according to any one of Claims 22 to 23, wherein the strong acid used is sulphuric acid.

25. A process according to any one of Claims 21 to 24, wherein R^7 represents (lower)alkyl, phenyl, monohalophenyl, dihalophenyl, monoalkylphenyl or dialkylphenyl.

26. A process according to any one of Claims 21 to 25, in which the compound of general formula:



is prepared by organosulphonylating a compound having the general formula:



where R^1 , R^2 , R^3 , R^4 and R^5 are as defined above.

27. A process according to Claim 13 substantially as described herein and shown with reference to the examples.

28. A process according to Claim 18 substantially as described herein and shown with reference to the examples.

29. A process according to Claim 21 substantially as described herein and shown with reference to the examples.

30. A compound prepared by a process according to any one of Claims 13 to 17 and 27.

31. A compound prepared by a process according to any one of Claims 18 to 20 and 28.

32. A compound prepared by a process according to any one of Claims 21 to 26 and 29.

33. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 12 and 30 to 32 in association with a pharmaceutically acceptable carrier.

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